from TNF- α and IL-6, depending on the degree of weight loss was not detected.

Abstract THU0457 – Figure 1. Dynamics of CRP depending on the degree of weight loss ($p < 0.05$)

Conclusion: The results of the study demonstrated a significant effectiveness of the complex treatment of obesity in patients with knee OA, compared with the use of only non-pharmacological methods of weight loss. A decrease in body mass of more than 5% helps to improve the clinical manifestations of knee OA and the quality of life of patients. A decrease in body weight of more than 10% demonstrates a decrease in the level of CRP, which suggests an effect on meta-inflammation in OA.

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THU0458

EFFICACY AND SAFETY FROM A PHASE 2B TRIAL OF SM04690, A NOVEL INTRA-ARTICULAR WNT PATHWAY INHIBITOR FOR THE TREATMENT OF OSTEOARTHRITIS OF THE KNEE

Yusuf Yazici¹, Timothy McAlindon², Allan Gibofsky³, Nancy Lane⁴, Christian Lattermann⁵, Nebojsa Skrepnik⁶, Christopher Swearingen¹, Anita DiFrancesco¹, Jeyanesh Tambiah¹, Marc Hochberg⁷. ¹Samumed, LLC, San Diego, United States of America; ²Tufts Medical Center, Boston, United States of America; ³Weill Cornell Medical College, New York, United States of America; ⁴UC Davis Medical Center, Davis, United States of America; ⁵Brigham and Women's Hospital, Boston, United States of America; ⁶Tucson Orthopedic Institute, Tucson, United States of America; ⁷University of Maryland School of Medicine, Baltimore, United States of America

Background: A phase 2a study of SM04690, a small-molecule, intra-articular (IA) Wnt pathway inhibitor reduced knee pain and improved physical function and medial joint space width (mJSW) at 52 weeks in subgroups of subjects with unilateral symptomatic knee osteoarthritis (OA) compared to placebo (PBO).¹

Objectives: A 24-week phase 2b study was conducted to refine patient-reported outcome (PRO) measures, target population, medication dose, and to evaluate safety. PRO results for Weeks 12 and 24 are presented here.

Methods: Study subject inclusion criteria required ACR-defined knee OA, Kellgren-Lawrence (KL) grades 2-3, and Pain Numeric Rating Scale (NRS) ≥ 4 and ≤ 8 in the target knee and < 4 in the contralateral knee. A single IA injection of 2 mL SM04690 (0.03, 0.07, 0.15, or 0.23 mg), vehicle PBO, or sham (dry needle only) was given in the target knee at baseline. PRO endpoints included change from baseline in weekly average of daily pain in the target knee by NRS diary (NRS) [0-10], Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain [0-100], WOMAC Physical Function [0-100], and Patient Global Assessment (PtGA) [0-100]. Differences between active treatment groups and vehicle PBO were analyzed with baseline-adjusted analysis of covariance (ANCOVA).

Results: 695 subjects (mean age 59.0 $\pm$ 8.5 years, BMI 29.0 $\pm$ 4.0 kg/m², female 58.4%, KL3 57.3%) were enrolled and dosed; 635 subjects (91.4%) completed the study. No meaningful differences in the incidence of adverse events were observed between treatment and control groups. In the Full Analysis Set, significant improvements from baseline compared to vehicle PBO were observed in pain NRS for 0.07 mg (Week 12 [$P=0.001$], Week 24 [$P=0.031$]) and 0.23 mg (Week 12 [$P=0.012$], Week 24 [$P=0.022$]) SM04690 dose groups (Figure). Similar improvements were observed in WOMAC Pain for 0.07 mg (Week 12 [$P=0.04$]) and 0.23 mg (Week 12 [$P=0.003$], Week 24 [$P=0.031$]) dose groups. For WOMAC Physical Function, improvements were observed for 0.07 mg (Week 12 [$p=0.021$]) and 0.23 mg (Week 12 [$p=0.006$], Week 24 [$P=0.017$]) dose groups. PtGA improvements were observed for 0.07 mg (Week 12

[$P=0.031$]) and 0.23 mg (Week 12 [$P=0.010$], Week 24 [$P=0.033$]) dose groups.

Conclusion: SM04690, in development as a potential disease-modifying OA drug, showed in this phase 2b study statistically significant improvements from baseline in both the 0.07 mg and 0.23 mg dose groups compared to vehicle PBO for Pain NRS, WOMAC Pain, WOMAC Physical Function, and PtGA. These data support the continued development of SM04690 as a treatment for knee OA. Phase 3 studies are being planned.

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Figure. Actual observations over time and ladder plots depicting least squares mean (LSM) improvement of Pain NRS ($\pm$ 95% CI) in SM04690 compared to vehicle PBO, adjusted for baseline.

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THU0459

PREDICTORS ASSOCIATED WITH RAPID PROGRESSION OF KNEE OSTEOARTHRITIS

Elena Taskina¹, Ludmila Alekseeva¹, Natalia Kashevarova¹, Sergey Anikin¹, Evgenia Sharapova¹, Ekaterina Strebkova¹, Lena Zonova², Tatiana Raskina³, Elvira Otteva⁴, Irina Vinogradova⁵, Aleksandr Lila¹. ¹V. A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation; ²FSBEI HE Novosibirsk State Medical University, Novosibirsk, Russian Federation; ³SBEI HE KemSMU MOH, Kemerovo, Russian Federation; ⁴Regional SBHI CDC MOH Khabarovsk kray, Khabarovsk, Russian Federation; ⁵SHI Ulyanovsk regional affiliated hospital, Ulyanovsk, Russian Federation

Objectives: To identify knee OA rapid progression factors in a multicenter prospective study

Methods: 185 female patients from 5 RF constituent territories aged 40-75 with confirmed Kellgren-Lawrence score grade I-III knee OA were included into prospective study after signing the informed consent form. Mean age was 59.2 $\pm$ 7.4 years (42-75), mean BMI=27.7 $\pm$ 4.4 kg/m², mean disease duration=12 $\pm$ 8.1 years. Individual patient's medical record included relevant anthropometric data, records from case history and clinical examination, VAS articular pain assessment, WOMAC scores, comorbidities. Instrumental diagnostic methods included plain radiography of knee joints, DEXA of the lumbar spine and femoral neck, MRI examination of knee joints. Stage II knee OA was established in 135 (73%) out of 185 patients, stage III – in 50 (27%).

Results: Knee OA progression (from radiographic stage II to stage III) within 1 year follow up was documented in 15 patients (Group 2 – with progressed OA), while 170 patients did not show any progression (Group 1 – no progression). Both groups were comparable in terms of age, age at RA onset, and duration of the disease. Although patients who progressed had higher body weight (97,1±14,0 vs 74,2±10,8 kg, $p<0,0001$) and BMI (31,9±5,8 vs 27,3±4,1 kg/m², $p<0,0001$). Patients from Group II had more intense knee pain during walking (VAS - 65,8±11,8 vs 47,5±18,7 mm ($p<0,0003$), and higher WOMAC: pain- 330,5±66,0 vs 237,8±85,4 mm, $p<0,0001$; function - 1044±190,4 vs 859,8±243,8 mm, $p<0,007$. Patients from Group II showed higher rates of varus knee alignment (66,7% vs 35,3%, $RR=1,89$, 95% CI 1,25-2,85, $p=0,02$) and H.valgus (86,7% vs 61,8%, $RR=1,4$, 95% CI 1,11-1,77, $p=0,04$), as well as higher rates of arterial hypertension (93,3% vs 71,8%, respectively, $RR=1,3$, 95% CI 1,1-1,53, $p=0,05$) and type 2 diabetes mellitus (DM) (33,3% vs 12,9%, $RR=2,57$, 95% CI 1,14-5,82, $p=0,04$). MRI showed higher percentage of medial and lateral tibia cartilage defects in Group 2 patients (57,2% vs 18,6%, respectively; $RR=3,06$, 95% CI 1,74-5,38, $p<0,003$; 57,2% vs 14%, $RR=4,08$, 95% CI 2,23-7,46 $p<0,0006$); bone marrow edema (BME) in medial (71,4% vs 12,2%, $RR=5,83$, 95% CI 3,38-10,1, $p<0,000004$) and lateral tibial compartments (21,4% vs 4,1%, $RR=5,25$, 95% CI 1,47-18,7, $p=0,03$); subchondral cysts, occupying more than 25% of the area in medial and lateral tibial compartments (respectively, 28,6% vs 7,4%, $RR=3,84$, 95% CI 1,4-10,5, $p<0,03$; and 35,7% vs 8,8%, $RR=4,06$, 95% CI 1,7-9,7, $p=0,01$). Synovitis (MRI findings) was documented in 100% patients from Group 2 and in 58,4% patients without OA progression ($RR=1,71$, 95% CI 1,5-2,0, $p=0,002$). A multivariate (discriminant) analysis showed that the most important risk factors for knee OA progression were: higher body weight, high WOMAC pain score, presence of type 2 DM, BME in medial tibial compartment, and cartilage damage in medial tibial compartment (MRI findings). A model capable of predicting rapid progression of knee OA in an individual patient with high accuracy (area under the ROC-curve 0,925 (95% CI 0,828–1,022)) has been developed based on identified RF and their coefficients.

Abstract THU0459 – Figure 1

Conclusion: In a prospective multicenter study, using comprehensive instrumental examination the following key predictors of rapid knee OA progression were identified: excessive body weight, high WOMAC pain score, presence of type 2 DM, BME in medial tibial compartment, and cartilage damage in medial tibial compartment (MRI findings).

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THU0460

IDENTIFICATION OF POSTOPERATIVE PAIN BIOMARKERS USING GENE EXPRESSION ANALYSES IN THE PERIPHERAL BLOOD OF OSTEOARTHRITIC PATIENTS PRIOR TO JOINT REPLACEMENT

Elena Tchetina¹, Kseniya Glemba², Sergey Makarov². ¹Nasonova Research Institute of Rheumatology, Immunology and Molecular Biology, Moscow, Russian Federation; ²Nasonova Research Institute of Rheumatology, Rheumoorthopaedic, Moscow, Russian Federation

Background: Osteoarthritis (OA) is a chronic rheumatic disease, which involves pain, limited inflammation and local destruction of the knee joint.

OA pain is a major clinical symptom, which limits working capacity and denotes an important indication for joint replacement in the end-stage OA. In spite of significant number of positive outcomes, chronic postoperative pain represents a major adverse consequence of surgery, which is observed in 10-40% of OA patients. Therefore, identification of patients potentially capable of developing chronic postoperative pain prior to surgery could significantly improve therapy outcome. Central sensitization is in charge of pain symptoms in about 30% of end-stage OA patients. Several recently identified molecular markers such as cytokines, chemokines, calcium and glutamate transporters, caspases, and proteases has been shown to be responsible for central sensitization. Therefore, we hypothesized that genes related to pain sensitization whose expression is upregulated in about 30% of the examined end-stage OA patient cohort might be responsible for postoperative pain.

Objectives: To outline an approach for search of biomarkers related to chronic postoperative pain development before joint replacement in the peripheral blood of end-stage OA patients.

Methods: We examined peripheral blood of 26 healthy volunteers (average age 55±8.3 years old) and 53 end-stage OA patients (average age 56.5±8.9 years old) undergoing joint replacement surgery. MMP-9, TIMP1, TGFβ1, and caspase 3 protein levels were quantified by ELISA. Total RNA isolated from whole blood was used in expression studies for the genes related to central sensitization such as mechanistic target of rapamycin, mTOR; caspase 3; metalloproteinase (MMP)-9; tissue inhibitor of metalloproteinase TIMP1; cathepsins K and S; interleukin (IL)-1β; cyclooxygenase (COX)2; tumor necrosis factor (TNF)α, and transforming growth (TGF)β1. These were performed with quantitative real-time RT-PCR.

Results: Retrospective analysis of gene expression in the peripheral blood of end-stage OA patients before joint replacement surgery revealed that gene expression data for TNFα, IL-1β, COX2, TGFβ1, and mTOR were not applicable as these gene expressions were significantly higher compared to healthy controls in all the examined OA patients. High expression of pain associated cathepsin S in 17% of the examined OA patients and cathepsin K, in 21% might indicate the possibility of postoperative pain development in these OA patients. In contrast, low expression of caspase 3 in 43% of the examined OA patients and MMP-9, in 23%, might point toward the absence of postoperative pain in these subjects.

Conclusion: Gene expression analysis in the peripheral blood of the end-stage OA patients measured before joint replacement surgery might represent an approach for prediction of postoperative pain development.

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THU0461

IDENTIFICATION OF DEFINITIONS OF POOR OUTCOME AFTER TREATMENT OF KNEE OSTEOARTHRITIS: A LITERATURE REVIEW

Malou te Molder¹, J.M.H. Smolders², Petra Heesterbeek³, Cornelia van den Ende⁴.

¹Sint Maartenskliniek, Research, Nijmegen, Netherlands; ²Sint Maartenskliniek, Orthopaedic Surgery, Nijmegen, Netherlands; ³Sint Maartenskliniek, Orthopaedic Research, Nijmegen, Netherlands; ⁴Sint Maartenskliniek, Rheumatology Research, Nijmegen, Netherlands

Background: Total knee replacement (TKR) is considered an effective intervention of the treatment of advanced knee osteoarthritis (OA) (Kellgren & Lawrence >2). However, a significant proportion of patients could be considered as a poor-responder to TKR (i.e. no or little improvement) in terms of chronic knee pain, functional disability, poor quality of life (QoL), and dissatisfaction after TKR. Both in research and in clinical practice it is challenging to identify those patients with an unfavourable course after TKR. It is difficult though to quantify the proportion of patients with poor response to TKR, as different definitions of, and perspectives (clinician's and patient's) on failure are being used.

Objectives: The aim of this study was to review the literature and summarize definitions of poor response to TKR.

Methods: A systematic search up to 2016 was performed to identify and review previously used definitions of poor response to primary TKR in the literature. Studies were included if dichotomous definitions of outcome after primary TKR were used, if a prospective design was used and in English full text available. The type, amount and combination of domains (i.e. pain and physical function), outcome measures, type of responses (absolute/relative, change/cut-off), values and moments of follow-up used in definitions were summarized.

Results: A total of 44 different dichotomous definitions of poor response to TKR, were extracted from 1849 initially identified studies. 34 definitions incorporated one domain, six definitions comprised two domains and four definitions comprised three domains. Eight different domains were used in identified definitions: pain, physical function (mobility), physical functioning